Usefulness of Aspirin for Primary Prevention of Atherosclerotic Cardiovascular Disease

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Aspirin use in the prevention of cardiovascular events has been a mainstay of treatment for decades. However, the use of aspirin in primary prevention of atherosclerotic cardiovascular disease has recently come under scrutiny. Several recent studies have evaluated the use of aspirin in primary prevention and the results suggest that in many patients the risks may outweigh the benefits. Closer examination of these trials suggests that the use of aspirin therapy for primary prevention may have a role but likely needs a more tailored approach and that caution is needed in prescribing aspirin for primary prevention. In conclusion, in this article we review the evolving evidence for aspirin in the primary prevention of atherosclerotic cardiovascular disease. **(Am J Cardiol 2019;124:1785−1789)**

Acetylsalicylic acid comes from the compound "salicin," meaning "willow" in Latin.[1] Galen and Hippocrates were two of the first to describe the antipyretic and anti-inflammatory effects of willow bark from which Henri Leroux would later isolate the compound "salicin" in the early 1800s. It was not until the 20th century that Lawrence Craven would discover that low doses of aspirin could prevent myocardial infarction (MI) and stroke,[2] which was later discovered to be through its ability to irreversibly inhibit COX-1 and the subsequent formation of prostaglandins and thromboxane A2 (promoters of platelet aggregation and vasoconstriction).[3] Since that time, aspirin has been widely studied for the use of prevention of atherosclerotic cardiovascular disease (ASCVD). Although the role of aspirin for secondary prevention of ASCVD has been well established in clinical trials, its use in primary prevention is more controversial, as seen in differing guidelines among professional societies. The aim of this study is to examine the evolving evidence of aspirin for primary prevention.

Review of Previously Published Reports

Aspirin's role in the secondary prevention of cardiovascular events is not in questions and should be continued unless there are significant contraindications. The first large trial to identify the role of aspirin in the prevention of ASCVD mortality and morbidity after MI was the International Study of Infarct Survival trial in 1988.[4] The use of aspirin resulted in a significant reduction in the rate of MI, stroke, vascular mortality, and all-cause mortality.[4] Much of this existing data has been compiled by the Antithrombotic Trials Collaboration. The results demonstrated that treatment over 2 years had an absolute risk reduction in patients who had a previous MI, stroke, or transient ischemic attack.[5]

In contrast to secondary prevention, the role of aspirin in primary prevention is more nuanced. Risk stratification is an important first step in determining appropriateness for aspirin therapy. Many population-based risk estimators exist such as the Framingham Risk Score, ASCVD risk calculator, Joint British Society risk calculator, and the World Health Organization risk charts. Risk calculators have a critical risk prediction tool and are the basis for many guidelines for risk stratification. The ASCVD calculator is an example of a pooled cohort equation (PCE)[6] that is designed to be gender- and race specific to identify modifiable risk,[7] and several recent guidelines including the 2018 Cholesterol Clinical Practice Guidelines[8] and the 2017 Hypertension Clinical Practice Guidelines[9] recommend the use of PCE to estimate the 10-year risk for ASCVD events.

Briefly reviewing some of the major earlier primary prevention trials dating back to the 1980s is important in understanding the evolution of aspirin in this era, as summarized in Table 1. A meta-analysis of the major earlier trials for the use of aspirin was not associated with a lower incidence of all-cause mortality ($p = 0.30$), but an increased incidence in major bleeding (relative risk (RR) 1.47) and intracranial hemorrhage (RR 1.33), confirming the lack of benefit of aspirin for all-cause mortality, and revealed the higher risk of bleeding in subjects without ASCVD risk.[10]

One of the early landmark studies was the Physicians Health Study, which revealed a reduction in the risk of MI in participants without cardiovascular disease who took aspirin,[11] but had a relative risk of gastric ulcers of 1.22. The British Doctor's Trial revealed a reduction in transient ischemic attacks in the aspirin group, but no difference in rates of fatal or nonfatal MI. Furthermore, the Women's Health Study revealed no significant effect on the risk of fatal or nonfatal MI ($p = 0.83$) or death from cardiovascular causes ($p = 0.68$) in the aspirin group. The Primary Prevention Project included both genders and an intention-to-treat analysis revealed that aspirin lowered the frequency of cardiovascular death as compared with placebo, but with a

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Table 1
Summary of the major primary prevention trials over the years for aspirin in primary prevention

Trial (Year)	Aspirin Dose (Daily, unless specified)	Control Group	Number of Subjects	Relative Risk (95% CI), Aspirin/Control Number of Events			
				Nonfatal MI	Nonfatal Stroke	Cardiovascular Mortality	All-Cause Mortality
BDT 1988	300-500 mg	No ASA	5,139	0.97 (0.67-1.41), 80/41	1.13 (0.72-1.77), 61/27	1.01 (0.74-1.37), 119/59	0.89 (0.74-1.08), 270/151
PHS 1989	325 mg alternate days	Placebo	22,071	0.59 (0.47-0.74), 129/213	1.20 (0.91-1.59), 110/92	0.92 (0.66-1.28), 66/72	0.96 (0.80-1.14), 217/227
PPP 2001	100 mg	No ASA	4,495	0.69 (0.36-1.33), 15/22	0.84 (0.42-1.67), 15/18	0.56 (0.31-1.01), 17/31	0.81 (0.58-1.13), 62/78
WHS 2005	100 mg alternate days	Placebo	39,876	1.01 (0.83-1.24), 184/181	0.81 (0.67-0.97), 198/244	0.95 (0.74-1.22), 120/126	0.95 (0.85-1.06), 609/642
JPAD 2008	100 mg	No ASA	2,539	1.35 (0.57-3.19), 12/9	1.01 (0.60-1.72), 27/27	0.10 (0.01-0.79), 1/10	0.91 (0.57-1.43), 33/38
POPADAD 2008	100 mg	Placebo	1,276	0.98 (0.69-1.40), 55/56	0.71 (0.45-1.12), 29/41	1.23 (0.80-1.89), 43/35	0.93 (0.72-1.21), 94/101
ARRIVE 2018	100 mg	Placebo	12,456	0.90 (0.81-1.13), 88/98	1.12 (0.80-1.55), 75/61* *Fatal or nonfatal	0.97 (0.62-1.52), 38/39	0.99 (0.80-1.24), 160/161
ASCEND 2018	100 mg	Placebo	15,480	0.98 (0.80-1.19), 191/195	0.88 (0.73-1.06), 202/229	**Any Vascular Event:** 0.88 (0.79-0.97), 658/743	**Any Major Bleeding:** 1.29 (1.09-1.52), 314/245
ASPREE 2018	100 mg	Placebo	19,114	**All Primary End Points$^{\Psi}$:** 1.01 (0.92-1.11), 921/914	**Persistent Physical Disability:** 0.85 (0.70-1.03), 188/224	**Major Hemorrhagic Event:** 1.38 (1.18-1.62), 361/265	**Death from Any Cause:** 1.14 (1.01-1.29), 558/494

The table highlights each study's population, number of participants, intervention (dosage of aspirin used), the primary endpoint, bleeding events, and all-cause mortality reported in the trials.
ARRIVE = Aspirin to Reduce Risk of Initial Vascular Event; ASA = Aspirin; ASCEND = Aspirin for Primary Prevention in Persons with Diabetes Mellitus; ASPREE = ASpirin in Reducing Events in the Elderly; BDT = British Doctor's Trial; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; MI = myocardial infarction; PHS = Physician Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; TIA = transient ischemic attack; UA = unstable angina; WHS = Women's Health Study; yo = years old.

significant increase in bleeding risk. These early trials did not show a significant reduction in overall cardiovascular mortality and raised concerns of an increase in side effect profile (gastric ulcers, bleeding, and disabling hemorrhagic stroke).

Patients with both type I and type II diabetes are a population at high risk for cardiovascular disease. The Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes revealed no difference in the primary end point of total atherosclerotic events in patients with type II diabetes without a history of atherosclerotic disease.[12] A similar trial, the Prevention of Progression of Arterial Disease and Diabetes trial did not provide evidence to support the use of aspirin or antioxidants in the primary prevention of ASCVD in patients with type I or type II diabetes.[13] In the Prevention of Progression of Arterial Disease and Diabetes trial, patients had asymptomatic periphral arterial disease and were already effectively treated with statin therapy, suggesting that aspirin may not have much benefit if statins are being used effectively.[13] Both of these trials were of relatively small populations and included patients with diabetes who had no prior ASCVD and low ASCVD risk profiles.

Expanding on these initial studies, recent randomized clinical trials have sought to answer the question whether the benefit of aspirin is worth the risk of bleeding. The Aspirin to Reduce Risk of Initial Vascular Event (ARRIVE) trial published in 2018 enrolled 12,456 patients with moderate ASCVD risk (mean Framingham Risk Score 10-year risk of ASCVD 17%) and no history of cardiac events.[14] In the intention-to-treat analysis, a primary cardiovascular event occurred in 4.29% of participants in the aspirin group versus 4.48% in the placebo arm. Of the individual components of the primary outcome, including MI (1.4% in aspirin vs 1.6% in placebo group) and stroke (1.2% with aspirin vs 1.1% with placebo) were not significantly different between the 2 groups. However, the risk of total and nonfatal MI (hazard ratio 0.53, and hazard ratio 0.55, respectively) was reduced by aspirin in the per-protocol analysis, and the relative risk reduction of MI in the aspirin group was 82.1% for those aged 50 to 59 years. Of note, gastrointestinal bleeding was twice as likely in the aspirin group compared with placebo, 0.97% versus 0.46% ($p = 0.0001$).[14] The event rates in this study were much lower than anticipated, making this essentially a trial of aspirin therapy in low-risk primary prevention patients who by all current guidelines would not have been offered aspirin therapy to begin with. Another important limitation of this study is that compliance with therapy among the aspirin group was only 60%, limiting the ability to draw definitive conclusions about the effectiveness of aspirin therapy in this trial. No conclusions about aspirin use in moderate- to high-risk patients can be drawn from this study given the low-risk population that was studied. The trial showed the significant risk of gastrointestinal (GI) bleeding with aspirin therapy, suggesting that lower risk patients may experience more adverse effects from aspirin therapy than benefits in primary prevention.

In 2018, The Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus trial (ASCEND)[15] randomized 15,480 patients with diabetes (any type) without ASCVD to aspirin 100 mg daily or placebo. During an

average 7.4 years follow-up, aspirin reduced the primary end point (first vascular event including MI, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage) by 12% in relative risk and 1.1% in absolute risk. Vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (8.5% vs 9.6%). This risk reduction was largely offset by an increase in major bleeding events in the aspirin group compared with placebo (4.1% vs 3.2%, RR 1.29, $p = 0.003$).[15] The major driver of the increased risk of bleeding in the aspirin group was gastrointestenial bleeding, and of these patients only approximately 25% were on a proton pump inhibitor, raising the question of whether increased use of proton pump inhibitors would mitigate the risk of bleeding.

The recently published Aspirin in Reducing Events in the Elderly trial (ASPREE)[16] examined whether 5 years of aspirin therapy extended disability-free years in the elderly (community-dwelling persons in Australia and the United States age 70 or older, or age 65 and older among blacks and Hispanics). This is the largest trial to date examining the effect of aspirin use in the elderly population. Of note, it was conducted in healthy seniors with low ASCVD risk. At a median follow-up of 4.7 years, the primary end point (composite of death, dementia, or persistent physical disability) was 21.5 events per 1,000 person-years in the aspirin group versus 21.2 per 1,000 person-years in the placebo group. The rate of cardiovascular events was 10.7 events per 1,000 person-years in the aspirin group and 11.3 events per 1,000 person-years in the placebo group. No significant differences in disability-free years were seen with the use of aspirin. Additionally, no major differences in ASCVD events were noted. The rate of major hemorrhage was higher in the aspirin group than in the placebo group at 3.8% versus 2.8%. The rate of GI bleeding was also twofold higher in the aspirin group, 2.1 events per 1,000 person-years versus 1.1 events per 1,000 person-years.[16] This study suggests that aspirin use in healthy elderly patients may result in harm with little benefit.

A meta-analysis of 13 randomized clinical trials (RCTs) which included the 3 most recent trials (Aspirin in Reducing Events in the Elderly, Aspirin for Primary Prevention in Persons with Diabetes Mellitus, and ARRIVE) looked at the association of aspirin use for primary prevention with ASCVD events and bleeding. Aspirin was found to be associated with reductions in composite ASCVD outcomes, absolute risk reduction 0.38%. However, aspirin use was found to be associated with increased major bleeding events, absolute risk increase 0.47% (95% confidence interval 0.34% to 0.62%) with number needed to harm of 210.[17] This meta-analysis is consistent with the previous data about the association of aspirin with ASCVD risk reduction and bleeding risk enhancement. The addition of these 3 new RCTs has not affected overall results significantly.[18]

Discussion

Data related to the use of aspirin in the primary prevention of ASCVD has evolved with several recent studies highlighting the need for caution in recommending aspirin to patients for primary prevention. Importantly, there are bleeding risks with aspirin use, and the ASCVD risk reduction in primary prevention appears to be modest. However, this does not necessarily mean there is no role for aspirin in primary prevention. As mentioned earlier, some of these studies had methodological flaws making it difficult to draw firm conclusions, including small population sizes, gender-specific studies, dosage variations, study populations with low- to moderate-risk profiles or populations with risk factors already well controlled with lifestyle interventions or statin use, and problems with compliance/adherence in certain trials. Furthermore, none of these studies examined high-risk primary prevention patients. For example, the observed cardiovascular event rate in the Aspirin to Reduce Risk of Initial Vascular Event trial was 9% instead of the expected 17% making this a relatively low-risk population. It is possible that high-risk (>20%) primary prevention patients would significantly benefit from daily aspirin therapy. In most of these trials, it was assumed that if the decrease in the ASCVD event rate was equal to the increased risk of nonfatal GI bleeding then this was considered a "negative" trial. However, it is not clear that patients or clinicians would agree with this stated equivalence.

Using risk estimator calculators and Pooled Cohort Equations (PCE) can be paramount in risk stratification for clinician and patient understanding. The American College of Cardiology/American Heart Association (ACC/AHA) Risk Estimator Plus[19] is an excellent application to estimate a patient's initial 10-year ASCVD risk and help guide discussion and customize individualized plans. Pooled Cohort Equations, although useful for quantifying risk and helping to guide discussion, may under- or overestimate risk in certain populations.[7] Although risk assessment calculators are the main stay of categorizing patients' risk, as it has been recommended for initiation of statin therapy risk-enhancing factors can be useful in stratifying at risk patients for ASCVD and using aspirin for primary prevention. These risk-enhancing factors include family history of premature ASCVD, persistently elevated Low Density Lipoprotein-Cholesterol (LDL-C) levels, metabolic syndrome, chronic inflammatory disorders, high-risk ethnic groups (South Asian), persistent elevation of triglycerides, additional biomarkers such as high-sensitivity C-reactive protein and apolipoprotein B, and ankle-brachial index.[8] The presence of these risk-enhancing factors increases the probability of ASCVD in an individual. For further clarity, and to resolve uncertainty in the decision process, certain noninvasive imaging modalities can also be used. The use of coronary artery calcium (CAC) score has been proposed as a tool to determine which primary prevention patients would benefit from aspirin therapy. One such study used the Multi-Ethnic Study of Atherosclerosis database to examine 4,229 nondiabetic patients not on aspirin therapy[20] and found that patients with CAC ≥100 had an estimated net benefit with aspirin, whereas, patients with CAC of 0 had estimated net harm. CAC scoring is one modality to assess the need for initiating aspirin therapy for primary prevention. Although not supported by guidelines, imaging modalities such as carotid ultrasound, arterial stiffness measurements, ankle-brachial index, and echocardiography to assess the atherosclerotic process may be used to gain additional clarity.[21]

The use of aspirin, like the use of statins, should first and foremost be risk based. The decision to initiate aspirin use

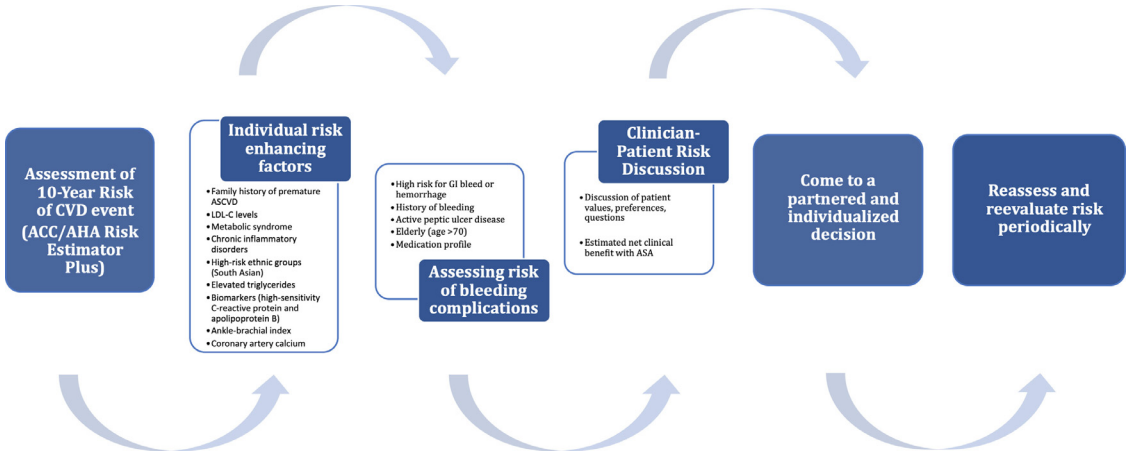

Figure 1. Use of Aspirin in Primary Prevention, A suggested approach to medical decision making.
A flow diagram suggesting an approach for the use of aspirin for primary prevention. Start with calculating the patient's 10-year risk for ASCVD using the ACC/AHA Risk Estimator Plus. Then proceed to evaluating a patient's individualized risk-enhancing factors and assess bleeding risk for that particular patient. Conduct a clinician patient risk discussion regarding risks and benefits including patient preferences. Finally, come to a partnered decision and continue to reassess and reevaluate risk in future visits.

should focus on net clinical benefit and be reevaluated periodically to reflect both the patient's preferences and present-day medical best practice (Figure 1). Each patient may vary in regard to their needs, values, and goals. There is strong evidence for shared decision making and how it can help successfully initiate dialogue between the patient and clinician to implement various guideline recommendations in primary prevention.[22] An effective clinician-patient risk discussion hinges on shared decision making and sufficient time should be given during clinical visits.

Use of aspirin should not be static and may need to be modified according to a patient's risk factors for ASCVD and/or adverse bleeding. If risk factors are well controlled with statins, smoking cessation, ACE inhibitors, and life style modifications then the risks of severe GI bleeding and hemorrhage may not be acceptable.[23] Furthermore, preventive therapy with statins potentially has a larger role in preventing ASCVD than aspirin use and has a more tolerable adverse risk profile.[23] It is also important to take into consideration that most risk assessment tools are intended to guide statin and antihypertensive therapy, although the quantitative risk score obtained can help delineate and stratify ASCVD risk to guide potential for aspirin use. There does not exist a single, validated tool to assess the potential benefits/risks for the use of aspirin. Perhaps an "AS-BLED" analogous to the "HAS-BLED" tool can be developed in the future to quickly and numerically assess and interpret individualized bleeding risks associated with aspirin therapy. Until then, the Aspirin Guide is an evidence-based, well-reviewed tool to estimate bleeding risk along with ASCVD risk score[24] which needs to be validated in literature. Importantly, with current management and risk reduction strategies, risk should be considered dynamic. If risk factors are well controlled, a patient's ASCVD risk may actually decrease over time.

In light of more evolving evidence and the three new major trials which have added further evidence for higher bleeding risk, the new ACC/AHA 2019 guidelines have recommended to consider low-dose aspirin (75 to 100 mg orally daily) among adults age 40 to 70 who are at a higher ASCVD risk but not at increased bleeding risk, and to withhold aspirin for primary prevention of ASCVD in adults over the age of 70 and among any patients who are at increased risk of bleeding.

Conclusion

The use of aspirin should not be a decision based entirely on a population-based number, but rather a careful, deliberated decision individualized for the patient. The notion that ASCVD is a dichotomous variable (either primary or secondary) is an appropriate starting point for classification, however, not sufficient. The primary prevention population is an extremely heterogeneous group of patients encompassing very low- to very high-risk patients. Although, earlier clinical trials in higher risk patients showed net clinical benefit of aspirin therapy, the more recent clinical trials in lower risk patients have been equivocal. So perhaps the question is not whether primary prevention patients should receive aspirin therapy, but rather which primary prevention patients should receive aspirin, and which should not. ASCVD risk is a spectrum and clinicians should move toward improved individualized risk assessment incorporating risk-enhancing factors and if needed CAC scoring. Until further trial evidence, aspirin use should likely be reserved for secondary prevention and high-risk (>20%) primary prevention patients or those with evidence of subclinical atherosclerosis after shared decision making focused on net clinical benefit.

Disclosures

Aneesha Thobani, Devinder S. Dhindsa, Benjamin D. DeMoss, Mohamad Raad, Pratik B. Sandesara, Laurence S. Sperling, and Jefferson T. Baer declare that they have no conflicts of interest.

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